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Impact of recurrent hospitalization for *Clostridioides difficile* on longitudinal outcomes in patients with inflammatory bowel diseases: a nationally representative cohort

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Abstract

Background: *Clostridioides difficile* infection (CDI) is associated with poor outcomes in patients with inflammatory bowel diseases (IBD).

Objectives: We conducted a nationally representative cohort study to evaluate the impact of recurrent CDI (rCDI)-related hospitalization on longitudinal unplanned healthcare utilization in patients with IBD.

Design: This was a retrospective cohort study that utilized the 2017 Nationwide Readmissions Database (NRD).

Methods: We identified 13,446 patients with IBD, hospitalized at least twice from January to June 2017 and followed through December 2017; of these, 1,148 had CDI-related hospitalizations. We compared the annual burden of hospitalization and IBD-related surgery in IBD patients with rCDI-related admission *versus* single CDI-related admission (primary reference), and those with one or more CDI-related admission *versus* no CDI-related admission (secondary reference).

Results: There were no significant differences in risk and burden of unplanned healthcare utilization (time spent in-hospital, 27 days *versus* 27 days, $p = 0.62$), 6-month readmission (63% *versus* 64.3%, $p = 0.8$) or IBD-related surgery in patients with recurrent (two or more) CDI-related hospitalizations *versus* single CDI-related admission. However, patients with ⩾1 CDI-related admission *versus* no CDI admissions experienced higher rate of 6-month readmission (61.1% *versus* 55.7%, $p < .001$), total days spent in the hospital per year (median: 26 days *versus* 21 days, $p < .001$), total cost across all hospitalizations per year ($212,524 *versus* $184,384, $p < 0.01$), and inpatient mortality (3.28% *versus* 1.81%, $p = 0.01$), without an increase in risk of IBD-related surgery (6.7% *versus* 6.4%, $p = 0.79$).

Conclusion: While patients with IBD hospitalized for CDI have poor longitudinal inpatient outcomes, recurrent admissions for CDI may not increase risk of adverse outcomes compared to one-time admission.

Keywords: infection, Crohn's disease, hospitalization, diarrhea

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Introduction

Clostridioides difficile infection (CDI) is the most common cause of diarrhea among hospitalized patients, and it results in substantial morbidity, mortality, and cost to the healthcare system.[1] In patients with inflammatory bowel diseases (IBD) including Crohn's disease and ulcerative colitis, *C. difficile* can cause a superimposed infectious

colitis, or precipitate an IBD flare. Though the national burden of CDI in the general population appears to be declining,[2] the incidence of CDI among hospitalized IBD patients has been on the rise.[3] This association is mediated by a multitude of factors, including recurrent hospitalizations and poor nutritional status among patients with IBD, which can increase risk of *C. difficile* acquisition and infection. Uncontrolled IBD, immunosuppression and antimicrobial agents use among the IBD population disrupt the intestinal flora and increase susceptibility to CDI.[4]

Compared to hospitalized IBD patients without CDI, patients with IBD hospitalized with CDI have inferior outcomes, including significantly increased in-hospital mortality, increased need for gastrointestinal surgery, and longer inpatient stays.[5,6] Relative to CDI, recurrent CDI (rCDI) incidence in the general population has increased; potential risk factors for rCDI that have been identified include older age, female sex, as well as recent use of antibiotics, corticosteroids, and proton-pump inhibitors.[7] Furthermore, patients with IBD are 33% more likely to experience rCDI compared with the general population; one can infer that this may be related to increased use of corticosteroids and antibiotics among patients with IBD.[8] Although it has been well established that IBD patients are more likely to have rCDI and have poor outcomes when hospitalized with CDI, data on comparative outcomes in IBD patients hospitalized with rCDI compared to those hospitalized with a single episode of CDI are lacking.

Hence, we conducted a retrospective cohort study to understand the impact of rCDI (*versus* single CDI *versus* no CDI-related hospitalization) on unplanned healthcare utilization in hospitalized patients with IBD. We used the Nationwide Readmissions Database (NRD) 2017, a longitudinal data set reflective of all-payer hospital readmissions in the United States, developed under the Healthcare Cost and Utilization Project (HCUP), to examine hospitalization-related burden, costs, mortality, risk of readmission and risk of IBD-related surgery among IBD patients with zero, one, or multiple hospitalizations for CDI.[9] We hypothesized that IBD patients with rCDI would have poor longitudinal outcomes compared to those hospitalized with single CDI, and that patients with a single CDI admission would have inferior outcomes compared to those with no CDI-related hospitalizations.

Methods

Study design and data source

This is a retrospective cohort study, designed using the NRD 2017. The database draws from 28 states disbursed geographically across the eastern, western and central U.S. regions, representing 60.0% of the U.S. population and 58.2% of all U.S. hospitalizations. It captures demographic, clinical, and nonclinical information on patients hospitalized in community, public, and academic medical centers over the course of a single year. After exclusions for missing or questionable patient linkage numbers and overlapping inpatient stays, the database accounts for 85% of discharges from the participating U.S. states.[10] Given that the NRD is a publicly accessible database containing de-identified patient information, this study was deemed exempt from Institutional Review Board evaluation and approval. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[11] The STROBE checklist items for cohort studies are listed in Supplemental Table 1. The overall study design including cohort selection, exposure determination, and outcome ascertainment is summarized in Figure 1(a).

Study population and exposure assessment

Using NRD 2017, we identified patients with IBD, with at least two hospital admissions between 1 January and 30 June 2017. These patients contributed to follow-up until the end of December 2017 or death. Since prior hospitalization is one of the strongest risk factors for recurrent hospitalization, including only patients with two or more hospital admissions allowed us to compare longitudinal outcomes in three cohorts of patients: patients hospitalized two or more times due to rCDI (exposure), patients hospitalized once with CDI and a second time for a non-CDI reason (*comparator #1*), and patients hospitalized twice for reasons unrelated to CDI (*comparator #2*). The second hospitalization was considered the index hospitalization, from which longitudinal outcome assessment was started. Our *primary analysis* compared patients with two or more CDI admissions to those with one CDI admission and a second non-CDI admission. Our *secondary analysis* compared patients with any CDI admission to those with no CDI admissions. Analysis groups are graphically represented in Figure 1(b).

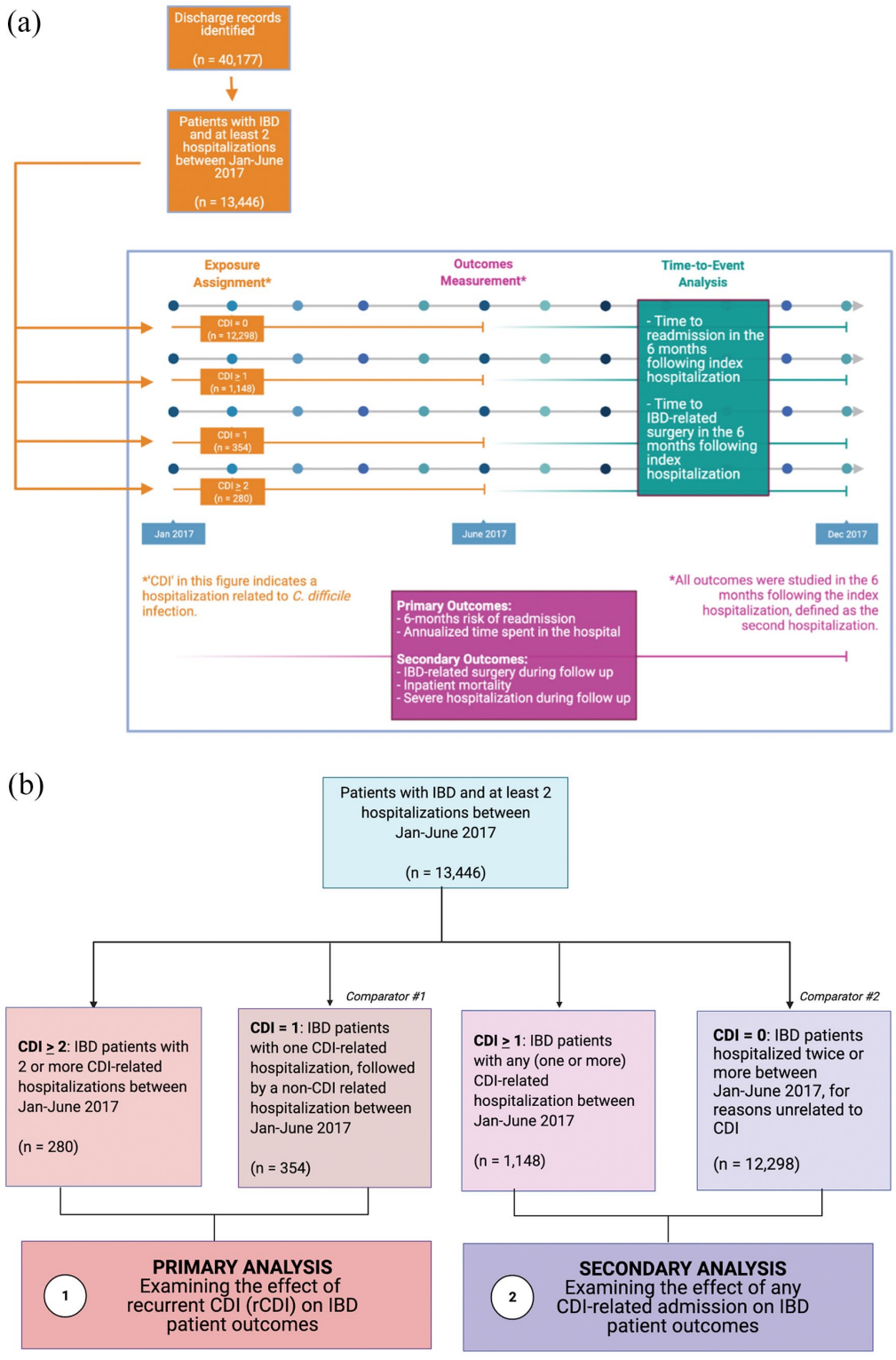

Figure 1. (a) Graphical representation of cohort study design (created with BioRender.com). Patients were selected based on exposure status (number of CDI-related hospitalizations from January to June 2017) and followed through December 2017 for measurement of primary and secondary outcomes of interest. Time-to-event analyses were performed, examining 6-month risk of readmission and IBD-related surgery from time of index hospitalization. (b) Graphical representation of primary and secondary analysis groups, based on exposure status (number of CDI-related hospitalizations from January to June 2017).
CDI, *Clostridioides difficile* infection; IBD, inflammatory bowel disease.

Patients with any diagnosis of IBD during the admission, as defined by the ICD-10 codes K50.x for Crohn's disease and K51.x for ulcerative colitis, were included in the analysis. We did not examine patients separately by IBD subtype (Crohn's disease, ulcerative colitis or unspecified IBD type) given inability to phenotype more deeply based on disease location, and lack of specific hypotheses where results would differ based on IBD subtype. Patients were deemed to have a CDI-related hospitalization if a diagnosis of *C. difficile* infection (ICD-10 code A04.7: Enterocolitis due to *Clostridium difficile*) was among the top five discharge diagnoses codes (out of 40 possible listed discharge diagnoses codes). We used International Classification of Diseases, 10th Revision-Clinical Modification (ICD-10-CM) to identify patients with IBD and to identify patients with *C. difficile* infection listed in their top five diagnoses.[12] Patients were required to have a minimum of 6 months of follow-up time to be included in the study. We excluded patients (1) with missing length of hospital stay, (2) who were transferred from another hospital, and (3) whose first IBD-related hospitalization was from 1 July to 31 December 2017.

Patient and hospital characteristics

We examined characteristics for each patient, including age, sex, primary expected payment source (Medicare/Medicaid, private insurance, self-pay, and other insurance types), income quartile based on household income of patient's zip code, index hospitalization length of stay, and relevant comorbidities to calculate the Charlson Comorbidity Index (CCI). The included comorbidities and coding algorithm used are displayed in Supplemental Table 2.[13,14] For each hospitalization, we captured IBD-related procedures such as endoscopy, colonoscopy, and flexible sigmoidoscopy, as well as IBD-related surgeries (colorectal resection, colostomy, ileostomy, etc.). For each hospital, we examined hospital location and teaching status. These baseline characteristics are summarized for our primary and secondary analyzes, in Tables 1 and 2, respectively.

Outcomes

The primary outcomes of interest were 6-month risk of readmission and annualized time spent in the hospital (total number of days spent in the hospital in 2017). Secondary outcomes examined (1) IBD-related surgery during follow-up, (2), inpatient mortality, and (3) severe hospitalization (length of stay >7 days or need for IBD-related surgery)[15] during follow-up. We also examined the time to readmission and time to IBD-related surgery in the 6 months following the index hospitalization. Preventable hospital admissions were characterized using ICD-10 codes for Prevention Quality Indicators. These are a set of measures developed by Agency for Healthcare Research and Quality that can be used with hospital inpatient discharge data as a screening tool to identify ambulatory conditions for which high-quality, community-based outpatient care can potentially prevent hospitalization, complications, or more severe disease. The above outcomes were compared between our primary and secondary analysis groups, as outlined in Figure 1(b).

Statistical analysis

We used descriptive statistics to compare patient demographics, admission characteristics, and hospital characteristics for the index hospitalization for IBD patients with 0, 1, or ≥ 2 hospitalizations with CDI. All hypothesis testing was performed with a 2-sided p value <0.05 indicating significance. We compared categorical variables using Pearson χ^2 test; Fisher's Exact test was employed where appropriate (i.e., where expected cell count was <5). Continuous variables were compared using Student t test and ANOVA. Categorical variables are expressed as percentages and continuous variables are expressed as median with an interquartile range. To evaluate the independent effect of single and rCDI-related admission on risk of 6-month readmission, we created two separate models. The *primary comparison* examined whether rCDI-related admission impacts the risk of 6-month readmission, compared to single CDI-related admission. The *secondary comparison* examined the effect of any CDI-related admission on risk of 6-month readmission, compared to no CDI-related admissions. The same models were utilized to examine risk of IBD-related surgery (as defined by the ICD-10 codes included in Supplemental Table 3) in the 6 months following index hospitalization. We performed multivariable Cox proportional hazard analysis using backward variable selection, adjusting for age, sex, length of stay at index hospitalization, CCI score, median household income, hospital urban status, hospital teaching status, primary payor, and severe IBD admission, to examine these outcomes. All

Table 1. Patient, hospital, and hospitalization characteristics of IBD patients with one CDI admission followed by subsequent non-CDI admission *versus* IBD patients with two or more CDI admissions, from January to June 2017.

Characteristics at time of index hospitalization	IBD patients with 1st visit CDI-related and 2nd non-CDI-related ($n = 354$)	IBD patients with two or more CDI-related admissions ($n = 280$)	*p* value
Age	50.1 (19.8)	53.5 (20.7)	0.04
Age by categories (%)			
Age < 40	129 (36.4%)	95 (33.9%)	0.0092
Age 40–64	133 (37.6%)	82 (29.3%)	
Age > 64	92 (26%)	103 (36.8%)	
Female (%)	207 (58.5%)	153 (54.6%)	0.38
Urban (%)	241 (68.1%)	180 (64.3%)	0.36
Primary expected payer (%)			
Medicare/Medicaid	206 (58.2%)	167 (59.6%)	0.84
Private insurance	131 (37%)	102 (36.4%)	
Others	17 (4.8%)	11 (3.93%)	
Median household income			
0–25th percentile ($1–$37,999)	92 (26.4%)	55 (19.8%)	0.28
26th–50th percentile ($38,000–$47,999)	91 (26.1%)	80 (28.8%)	
51st–75th percentile ($48,000–$63,999)	92 (26.4%)	77 (27.7%)	
76th–100th percentile ($64,000 or more)	74 (21.2%)	66 (23.7%)	
Teaching status (%)			
Metropolitan non-teaching	66 (18.6%)	60 (21.4%)	0.46
Metropolitan teaching	276 (78%)	207 (73.9%)	
Non-metropolitan	12 (3.39%)	13 (4.64%)	
IBD-related procedures (%)	47 (13.3%)	47 (16.8%)	0.26
IBD-related surgeries (%)	23 (6.5%)	15 (5.36%)	0.67
Deyo-CCI (%)			
0	180 (50.8%)	125 (44.6%)	0.07
1	59 (16.7%)	67 (23.9%)	
2 or more	115 (32.5%)	88 (31.4%)	
Length of stay in days, Median [Interquartile range (IQR)]	4 (4)	5 (6)	0.0039
Proportion with severe IBD hospitalization [Length of stay (LOS) > 7 days or surgery] (%)	98 (27.7%)	109 (38.9%)	0.0036

Table 2. Patient, hospital, and hospitalization characteristics of IBD patients with any CDI admission (one or more) *versus* IBD patients with no CDI admissions, from January to June 2017.

Characteristics at time of index hospitalization	IBD patients with no CDI-related hospitalizations among first 2 visits (*n* = 12,298)	IBD patients with one or more CDI-related hospitalizations among first 2 visits (*n* = 1148)	*p* Value
Age	52.4 (19.3)	52.5 (20.4)	0.87
Age by categories (%)			
Age < 40	3846 (31.3%)	383 (33.4%)	0.01
Age 40–64	4730 (38.5%)	390 (34%)	
Age > 64	3722 (30.3%)	375 (32.7%)	
Female (%)	6691 (54.4%)	645 (56.2%)	0.26
Urban (%)	7657 (62.3%)	755 (65.8%)	0.02
Primary expected payer (%)			
Medicare/Medicaid	7339 (59.7%)	687 (59.8%)	0.63
Private insurance	4176 (34%)	396 (34.5%)	
Others	783 (6.37%)	65 (5.66%)	
Median household income			
0–25th percentile ($1–$37,999)	3077 (25.3%)	267 (23.6%)	0.57
26th–50th percentile ($38,000–$47,999)	3222 (26.5%)	298 (26.4%)	
51st–75th percentile ($48,000–$63,999)	3121 (25.7%)	305 (27%)	
76th–100th percentile ($64,000 or more)	2732 (22.5%)	260 (23%)	
Teaching status (%)			
Metropolitan non-teaching	2705 (22%)	233 (20.3%)	0.08
Metropolitan teaching	8931 (72.6%)	866 (75.4%)	
Non-metropolitan	662 (5.38%)	49 (4.27%)	
IBD-related procedures (%)	960 (7.81%)	149 (13%)	<0.001
IBD-related surgeries (%)	688 (5.59%)	53 (4.62%)	0.19
Deyo-CCI (%)			
0	5587 (45.4%)	542 (47.2%)	0.39
1	2377 (19.3%)	224 (19.5%)	
2 or more	4334 (35.2%)	382 (33.3%)	
Length of stay in days, Median (IQR)	4 (4)	5 (6)	<0.001
Proportion with severe IBD hospitalization (LOS > 7 days or surgery) (%)	3314 (26.9%)	428 (37.3%)	<0.001

Table 3. Longitudinal outcomes in IBD patients with one CDI admission followed by subsequent non-CDI admission, *versus* IBD patients with two or more CDI admissions, from January to June 2017.

Outcomes during follow up (within 6 months of index hospitalization)	IBD patients with 1st visit being CDI-related and second non-CDI-related ($n = 354$)	IBD patients with first 2 visits being CDI-related ($n = 280$)	*p* Value
Readmission (%)	223 (63%)	180 (64.3%)	0.8
Inpatient mortality (%)	NR[a]	NR[a]	0.14
Severe hospitalization (LOS > 7 days or need for IBD-related surgery) (%)	78 (35%)	59 (32.8%)	0.72
Unplanned hospitalization (%)	201 (90.1%)	164 (91.1%)	0.87
Preventable hospitalization (%)	NR[a]	NR[a]	0.79
IBD-related procedures (%)	19 (8.52%)	19 (10.6%)	0.6
IBD-related surgery (%)	NR[a]	NR[a]	0.89
Annual burden and costs of hospitalization: Total follow-up time (months), median (IQR)	2 (2)	1 (2)	0.89
Annual days spent in the hospital (including during index hospitalization), median (IQR)	27 (28)	27 (21)	0.62
Annual costs across all hospitalizations (in dollars), median (IQR)	223,296 (262,127)	183,786 (231,667)	0.23

[a]Due to <11 events per cell, we cannot report counts per HCUP data use policy.

statistical analyses were performed using R Statistical Software version 4.1.0 (Foundation for Statistical Computing, Vienna, Austria).

Results

Of the 17,978,754 discharge records analyzed in NRD 2017, 40,177 (patients with two or more hospital admissions) were identified for analysis, representing 13,446 individual patients with a diagnosis of IBD and at least two hospitalizations between January and June of 2017. Of these, 12,298 patients (91.5%) had zero CDI-related hospitalizations, 1,148 patients (8.5%) had one or more CDI-related hospitalizations among the first 2 visits, 354 patients (2.6%) had one CDI-related hospitalization and a second non-CDI-related hospitalization, and 280 patients (2.1%) had two or more CDI-related hospitalizations.

Outcomes in patients with ⩾2 CDI-related admissions versus *one CDI-related admission*

We did not observe any significant increase in the risk of readmission (63% *versus* 64.3%, $p = 0.8$), IBD-related surgery ($p = 0.89$), inpatient mortality ($p = 0.14$), or risk of severe hospitalization (35% *versus* 32.8%, $p = 0.72$) in patients with two or more CDI-related admissions compared with those with only one CDI-related admission in the defined follow-up period (Table 3). Figure 2 demonstrates survival curves for time to readmission in patients with ⩾2 CDI-related admissions *versus* one CDI admission. Similarly, no significant difference in annual burden of hospitalization [27 days (28) *versus* 27 days (21), $p = 0.62$], or annual cost across all hospitalizations [$223,296 (262,127) *versus* $183,786 (231,667), $p = 0.23$] was observed.

On multivariable analysis, adjusting for age, sex, length of stay at index hospitalization, CCI score, median household income, hospital urban status, hospital teaching status, primary payor, and severe IBD admission, rCDI-related admission was not associated with shorter time to readmission compared with patients with only one CDI-related admission [hazard ratio (HR), 1.04; 95% CI, 0.85, 1.27] (Table 4). We were unable to perform multivariate analysis to assess IBD-related

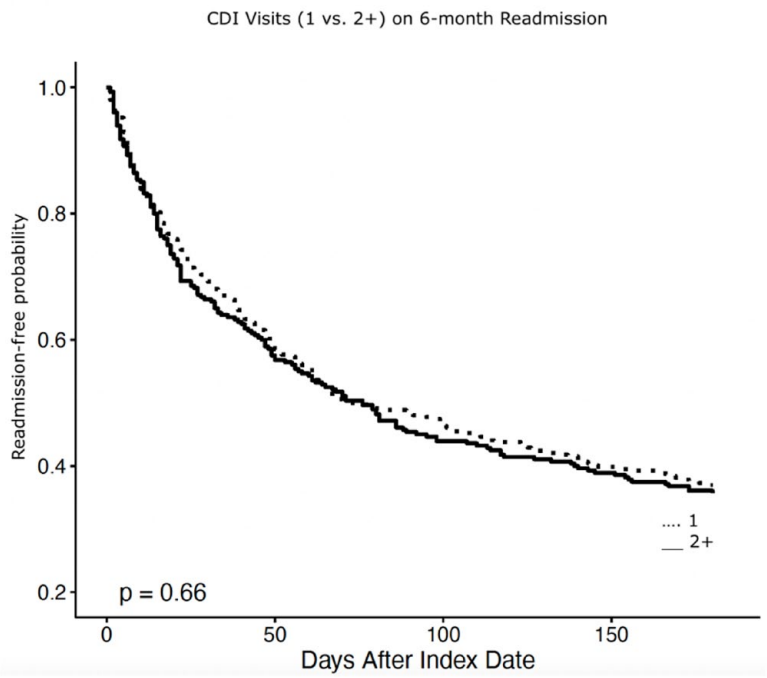

Figure 2. Kaplan–Meier curve demonstrating 6-month readmission probability in IBD patients with single *versus* recurrent *C. difficile* (CDI)-related hospitalizations.

surgery risk in patients with rCDI-related admission *versus* one CDI-related admission, given too few events per category.

Outcomes in patients with ⩾1 CDI-related admissions versus *non-CDI-related admissions*

Compared to patients with no CDI admissions among their first hospitalizations, patients with IBD and ⩾1 CDI hospitalization had a significantly higher rate of 6-month readmission (61.1% *versus* 55.7%, $p < 0.001$), unplanned hospitalization (90.2% *versus* 86.5%, $p < 0.01$), IBD-related procedures (10% *versus* 6.3%, $p < 0.001$), inpatient mortality (3.3% *versus* 1.8%, $p = 0.01$), and rate of severe hospitalizations (34.9% *versus* 30.4%, $p = 0.02$). However, no differences were observed in risk of IBD-related surgery (6.7% *versus* 6.4%, $p = 0.79$) (Table 5). Figure 3(a) and (b) demonstrate survival curves for time to readmission and IBD-related surgery in patients with ⩾1 CDI admissions *versus* non-CDI-related admissions. Patients with IBD with one or more CDI-related hospitalization also spent more time in the hospital per year [median (interquartile range): 26 days (23) *versus* 21 days (22), $p < 0.001$] and had higher annual costs of hospitalizations [$212,524 (246,538) *versus* $184,384 (225,090), $p < 0.01$].

On multivariable analysis, adjusting for age, sex, length of stay at index hospitalization, CCI score, median household income, hospital urban status, hospital teaching status, and primary payor, having one or more CDI-related hospitalizations was associated with a 16% higher risk of readmission in the 6 months following index hospitalization [adjusted hazard ratio (aHR), 1.16; 95% confidence interval (CI), 1.07–1.26] compared with patients with non-CDI-related admissions (Table 6). However, having one or more CDI-related hospitalization was not associated with an increase in the risk of IBD-related surgery (Table 7). As severe IBD hospitalization was strongly predictive of IBD-related surgery, severe IBD admission was not included as a covariate in this particular model.

Discussion

Few studies have examined morbidity and mortality associated with rCDI-related hospitalization in patients with IBD. In this study, we confirmed prior findings that being hospitalized with CDI was associated with increased inpatient mortality, IBD-related procedures, and overall days spent in the hospital for patients with IBD. Patients with IBD who were hospitalized for CDI at least once were at significantly, albeit modestly, higher risk for readmission in the subsequent 6 months compared to those admitted to the hospital for other, non-CDI-related reasons, after adjusting for important covariates. This supports our hypothesis and was to be anticipated based on the existing body of literature that also supports these findings; Jen *et al.* found that patients with IBD admitted to NHS hospitals in England with co-existent CDI were at greater risk of in-hospital mortality and had longer inpatient stays and gastrointestinal surgery rates compared to patients admitted for IBD alone. Nguyen *et al.* also found that CDI was associated with increased length of stay and hospital charges among hospitalized IBD patients, compared to that in those uninfected with *C. difficile*.[5,16] However, contrary to our hypothesis, recurrent hospitalization for *C. difficile* was not specifically associated with worse outcomes compared to patients who experienced only one CDI-related admission, after controlling for number of hospitalizations. One possible explanation for this can be deduced upon

Table 4. Cox proportional hazard analysis evaluating time-to-readmission within 6 months of index hospitalization, for IBD patients with single *versus* recurrent CDI admissions from January to June 2017.

Variable	Hazard ratio (95% confidence interval)	*p* Value	Proportional hazards assumption test *p* value
Single *versus* recurrent CDI-related admissions in the first 6 months	1.042 (0.852, 1.274)	0.692	0.781
Age (per 1-year increase)	0.995 (0.989, 1.001)	0.111	0.155
Sex (male *versus* female)	1.074 (0.877, 1.316)	0.489	0.509
Length of stay at index hospitalization (per 1-day increase)	1.009 (0.988, 1.03)	0.397	0.375
CCI (reference group: 0)			0.871
1	1.024 (0.774, 1.356)	0.866	
2 or more	1.242 (0.944, 1.635)	0.122	
Median household income (reference group: 0 to 25th percentile ($1–$37,999))			0.948
26th–50th percentile ($44,000–$55,999)	1.228 (0.927, 1.628)	0.153	
51th–75th percentile ($56,000–$73,999)	0.922 (0.688, 1.235)	0.584	
76th–100th percentile ($74,000 or more)	1.186 (0.871, 1.615)	0.278	
Urban (reference group: Rural)	1.105 (0.879, 1.39)	0.392	0.800
Primary expected payer (reference group: Medicare/ Medicaid)			0.240
Private insurance	0.862 (0.681, 1.09)	0.215	
Others	1.227 (0.761, 1.976)	0.401	
Teaching status (reference group: Metropolitan non-teaching)			0.552
Metropolitan teaching	1.091 (0.843, 1.414)	0.507	
Non-metropolitan	1.146 (0.644, 2.042)	0.643	
Severe IBD hospitalization (reference group: no severe hospitalization)	1.104 (0.829, 1.47)	0.499	0.132
Global proportional hazards assumption test			0.909

closer examination of the relationship between *C. difficile* and IBD. Studies have reported that patients with IBD have significantly higher rates of asymptomatic *C. difficile* carriage compared to healthy individuals[4,17]; moreover, it is challenging to reliably distinguish true CDI from an IBD flare given the similarity in symptoms between the two.[4,18] Thus, it is possible that the hospitalizations in our study presumed secondary to CDI recurrence were, in fact, related primarily to an alternative diagnosis. Because the IBD population is so frequently surveilled for CDI and is more likely to be colonized by *C. difficile*, these hospitalizations may have been mistakenly attributed to CDI due to incidental isolation of *C. difficile* on antigen testing. Related to this, our study defined hospitalization for CDI by a diagnosis of *C. difficile* in the top 5 discharge diagnoses; no distinction was made between a primary or secondary diagnosis for rCDI. Another study, albeit

Table 5. Longitudinal outcomes in IBD patients with any CDI admission (one or more) *versus* IBD patients with no CDI admissions, from January to June 2017.

Outcomes during follow up (within 6 months of index hospitalization)	IBD patients with no CDI-related hospitalizations among first 2 visits ($n = 12,298$)	IBD patients with one or more CDI-related hospitalizations among first 2 visits ($n = 1148$)	*p* Value
Readmission (%)	6851 (55.7%)	702 (61.1%)	<0.001
Inpatient mortality (%)	124 (1.81%)	23 (3.28%)	0.01
Severe hospitalization (LOS > 7 days or need for IBD-related surgery) (%)	2084 (30.4%)	245 (34.9%)	0.02
Unplanned hospitalization (%)	5915 (86.5%)	633 (90.2%)	0.007
Preventable hospitalization (%)	365 (5.33%)	21 (3%)	0.01
IBD-related procedures (%)	429 (6.26%)	70 (9.97%)	<0.001
IBD-related surgery (%)	436 (6.36%)	47 (6.7%)	0.79
Annual burden and costs of hospitalization: Total follow-up time (months), median (IQR)	1 (2)	2 (2)	0.78
Annual days spent in the hospital (including during index hospitalization), median (IQR)	21 (22)	26 (23)	<0.001
Annual costs across all hospitalizations (in dollars), median (IQR)	184,384 (225,090)	212,524 (246,538)	0.0049

IQR, Interquartile range; LOS, Length of stay.

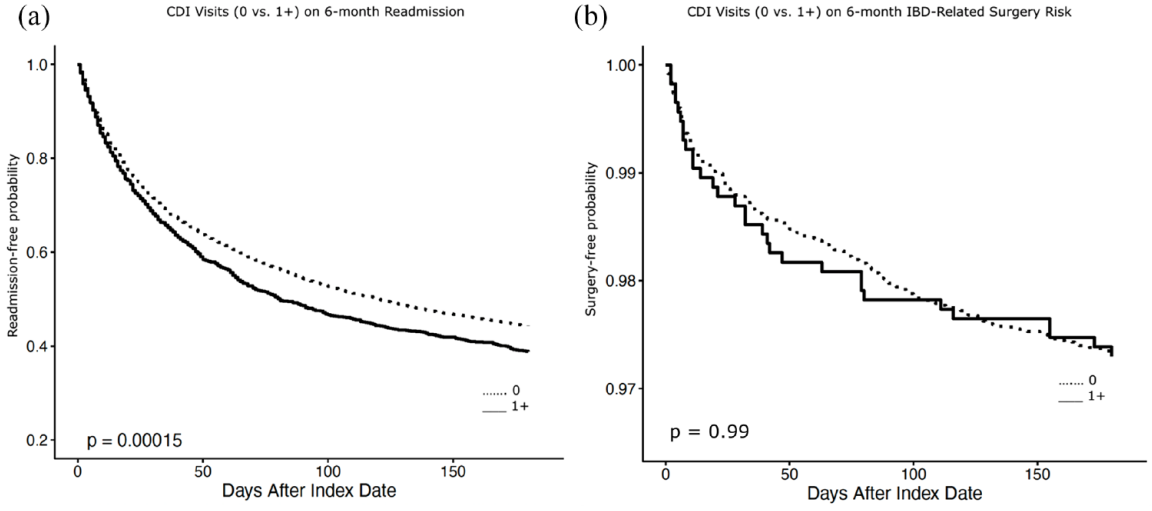

Figure 3. (a) Kaplan–Meier curve demonstrating 6-month readmission probability in IBD patients with zero *versus* one or more *C. difficile* (CDI)-related hospitalizations. (b) Kaplan–Meier curve demonstrating 6-month IBD-related surgery probability in IBD patients with zero *versus* one or more *C. difficile* (CDI)-related hospitalizations.

in a non-IBD patient population, did make this distinction with regard to rCDI and found that an increase in mortality observed among patients with a secondary diagnosis of rCDI was largely driven by alternative primary admission diagnoses (e.g., sepsis). When primary and secondary

Table 6. Cox proportional hazard analysis evaluating time-to-readmission within 6 months of index hospitalization, for IBD patients with no CDI admissions *versus* those with one or more CDI admissions from January to June 2017.

Variable	Hazard ratio (95% CI)	*p* Value	Proportional hazards assumption test *p* value
Zero *versus* one or more CDI-related admissions in the first 6 months	1.16 (1.072, 1.255)	<0.001	0.878
Age (per 1-year increase)	0.994 (0.992, 0.995)	<0.001	0.006
Sex (male *versus* female)	1.018 (0.973, 1.066)	0.441	0.033
Length of stay at index hospitalization (per 1-day increase)	1.007 (1.003, 1.012)	0.002	<0.001
CCI (reference group: 0)			0.27
1	1.127 (1.056, 1.202)	<0.001	
2 or more	1.367 (1.288, 1.452)	<0.001	
Median household income (reference group: 0 to 25th percentile ($1–$37,999))			0.048
26th–50th percentile ($44,000–$55,999)	0.986 (0.926, 1.049)	0.654	
51th–75th percentile ($56,000–$73,999)	0.918 (0.861, 0.979)	0.0096	
76th–100th percentile ($74,000 or more)	0.923 (0.861, 0.99)	0.0024	
Urban (reference group: Rural)	1.042 (0.989, 1.097)	0.121	0.36
Primary expected payer (reference group: Medicare/Medicaid)			0.753
Private insurance	0.743 (0.702, 0.785)	<0.001	
Others	0.964 (0.876, 1.062)	0.462	
Teaching status (reference group: Metropolitan non-teaching)			0.131
Metropolitan teaching	1.04 (0.983, 1.101)	0.169	
Non-metropolitan	0.846 (0.75, 0.953)	0.006	
Severe IBD hospitalization (reference group: no severe hospitalization)	1.023 (0.958, 1.093)	0.492	0.003
Global proportional hazards assumption test			<0.001

diagnoses for rCDI were examined separately, no significant difference in mortality was seen between patients with single *versus* recurrent primary CDI-related hospitalization.[19] Another possibility, in theory, is that initial alterations to the gut microbiome caused by CDI in patients with IBD are more deleterious compared to subsequent alterations introduced by rCDI, resulting in no significant increase in risk of adverse outcomes with recurrent infection. There are some data to suggest that IBD patients who go on to develop rCDI possess a distinct microbial community structure compared to non-rCDI patients[20]; however, more research is needed to determine to what extent microbiome changes drive long-term outcomes, and what effect these changes have on illness severity.

The strengths of our study include (1) innovative use of a nationally representative database with

Table 7. Cox proportional hazard analysis evaluating risk of IBD-related surgery within 6 months of index hospitalization, for IBD patients with no CDI admissions *versus* those with one or more CDI admissions from January to June 2017.

Variable	Hazard ratio (95% CI)	*p* Value	Proportional hazards assumption test *p* value
Zero *versus* one or more CDI-related admissions in the first 6 months	0.871 (0.599, 1.266)	0.468	0.473
Age (per 1-year increase)	0.994 (0.987, 1.001)	0.083	0.025
Sex (male *versus* female)	0.891 (0.722, 1.098)	0.278	0.77
Length of stay at index hospitalization (per 1-day increase)	1.058 (1.051, 1.065)	<0.001	0.318
CCI (reference group: 0)			0.722
1	0.732 (0.547, 0.98)	0.036	
2 or more	0.446 (0.328, 0.605)	<0.001	
Median household income (reference group: 0 to 25th percentile ($1–$37,999))			0.855
26th–50th percentile ($44,000–$55,999)	0.807 (0.595, 1.095)	0.168	
51th–75th percentile ($56,000–$73,999)	0.892 (0.664, 1.198)	0.446	
76th–100th percentile ($74,000 or more)	0.959 (0.706, 1.304)	0.79	
Urban (reference group: Rural)	1.031 (0.816, 1.303)	0.797	0.015
Primary expected payer (reference group: Medicare/ Medicaid)			0.599
Private insurance	1.664 (1.314, 2.107)	<0.001	
Others	0.94 (0.571, 1.549)	0.809	
Teaching status (reference group: Metropolitan non-teaching)			0.003
Metropolitan teaching	1.585 (1.171, 2.145)	0.003	
Non-metropolitan	0.657 (0.294, 1.468)	0.305	
Global proportional hazards assumption test			0.038

high generalizability, designed specifically for the study of readmission risk and hospital-related outcomes, (2) code-based classification and interpretation of rCDI-related hospitalizations to allow for independent assessment of outcomes in the setting of *C. difficile* recurrence, (3) thorough evaluation of multiple adverse health outcomes around unplanned healthcare utilization, with adjustment for important confounding variables, and (4) mitigation of bias by using a control group consisting of IBD patients hospitalized at least twice in 2017 for non-CDI-related reasons, in order to better distinguish differences in outcomes related to CDI hospitalization *versus* re-hospitalization for alternative reasons.

Our study has a few key limitations to consider. First, the analysis was based on administrative codes, which are subject to misclassification of IBD and of CDI, as well as human error. Second, for admissions coded to reflect a diagnosis of CDI, there is no distinction made between acquired CDI or a history of CDI; sometimes, a diagnosis of CDI is carried forward to a subsequent hospitalization as there is no diagnosis code available for a history of *C. difficile*. Though it is

possible to perform further sub-coding to help identify rCDI, this does not provide information on timing, frequency, or severity of recurrences; as such, we instead opted to utilize the parent ICD-10 code for CDI and focus on hospitalized CDI as a measure of recurrence. Hospitalizations were only considered CDI-related if a diagnosis of *C. difficile* was among the top 5 discharge diagnoses; thus, it is possible that some cases of CDI were missed given the lack of comprehensive inclusion of all discharge diagnoses. Third, rCDI is defined by a return of diarrheal symptoms within 8 weeks of an initial infection, associated with a positive assay result, with resolution of symptoms in the interim[21]; however, it is not possible to determine timing of symptoms in the NRD, and recurrent hospitalizations for CDI could thus potentially represent persistent or incompletely resolved initial CDI. Future studies may utilize a minimum required time frame between admissions in an effort to mitigate this. As discussed above, the challenge of accurately diagnosing *C. difficile* and distinguishing true CDI from IBD flare also poses a limitation to the study results. Fourth, this study does not capture outpatient resource utilization or costs, nor take into consideration other factors impacting risk of CDI including recent antibiotic use, medication regimen, medication adherence, disease duration, location or presence of complications, markers of disease severity and activity, or history of/previous hospitalization for CDI prior to 2017. Finally, the NRD is inherently limited as it only captures admissions within state boundaries, does not capture out-of-hospital mortality, and limits our ability to longitudinally track patient outcomes to a one-year follow-up period.

In summary, we observed that among patients with IBD, admission to the hospital specifically for CDI is associated with higher inpatient mortality, number of days spent in the hospital annually, risk of unplanned hospitalization, risk of readmission and risk of IBD-related procedures compared to those hospitalized for a non-CDI-related reason. However, being hospitalized again for *C. difficile* after an initial CDI-related admission does not appear to further increase risk of the outcomes examined in our study population. This could be in part due to misclassification of CDI episodes, though more studies are needed with large enough sample size among IBD patients with rCDI, in order to examine this more closely and perform adequately powered stratified analyzes. Future studies may replicate the methods employed in this study to further examine this important clinical question. A larger body of evidence examining the long-term implications of rCDI hospitalization in IBD patients can inform how aggressively IBD specialists should pursue therapies to prevent CDI recurrence, such as fecal microbiota transplantation, in clinical practice.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contribution(s)

Preethi G. Venkat: Data curation; Investigation; Writing – original draft.

Nghia H. Nguyen: Conceptualization; Data curation; Formal analysis; Writing – review & editing.

Jiyu Luo: Data curation; Formal analysis; Writing – review & editing.

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Competing interests

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Availability of data and materials

The NRD is a publicly available database that can be purchased through the HCUP Central Distributor. The NRD is available for data years 2010–2019.

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Supplemental material

Supplemental material for this article is available online.

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